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Betula utilis extends lifespan & attenuates age related amyloid-beta induced toxicity in Caenorhabditis elegans

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Betula utilis (BU) is an important medicinal plant that grows in high altitudes of the Himalayan region (4,500 m), and has been utilized traditionally due to its antibacterial, hepatoprotective, and anti-tumor properties. Here, we demonstrated the longevity and amyloid-β toxicity attenuating activity of *B. utilis* ethanolic extract (BUE) in *Caenorhabditis elegans*. Amyloid-β, one of the hallmarks of Alzheimer's disease, is toxic to neurons and causes cell death in the brain. Lifespan of the worms was observed under both the standard laboratory and oxidative and thermal stress conditions. The non-targeted qualitative and quantitative analysis of the ethanolic extract of (BU) was performed through Gas Chromatography-Mass Spectrometry with three replicates. Chromatographic separations of metabolites were carried out using the characterization of individual metabolites. The potential of BUE was also observed on the several parameters like toxicity assay, lifespan analysis, stress resistance assay, pharyngeal pumping analysis, chemotaxis behavior assay, measurement of intracellular ROS, analysis of alpha-synuclein accumulation, worm paralysis assay, aldicarb sensitivity assay, lipofuscin assay and green fluorescent protein visualization assay. Our results showed that BUE (50 µg/ml) can enhance the mean lifespan of *C. elegans* by 35.99% extensively and improved its endurance under stress conditions. The BUE also reduced the levels of intracellular reactive oxygen species (ROS) by 22.47%. A delayed amyloid-β induced paralyses was observed in CL4176 transgenic worms. Interestingly, the BUE supplementation was also able to reduce the α-synuclein aggregation in NL5901 transgenic strain. Gene-specific mutant studies suggested that the BUE-mediated lifespan extension was dependent on *daf-16, hsf-1,* and *skn-1* but not on *sir-2.1* gene. Furthermore, transgenic reporter gene expression assay showed that BUE treatment enhanced the expression of stress-protective genes such as *sod-3* and *gst-4*. Present findings suggested that ROS scavenging activity, together with multiple longevity mechanisms, were involved in BUE-mediated lifespan extension. Thus, BUE might have potential to increase the lifespan and to attenuate neuro-related disease progression.

Keywords: Aging, Neuroprotection, Alzheimers, Parkinsons, *C. elegans*